65. (New) An isolated nucleic acid molecule which encodes a protein comprising the amino acid sequence of SEQ ID NO:4.

66. (New) The isolated nucleic acid molecule of claim 52, which encoded the amino acid sequence of SEQ ID NO:4 but for the mutation at least one codon of the nucleic acid molecule encoding amino acids 871-874 of SEQ ID NO:4.

REMARKS

Claims 1-8, 12, 16, 19, 20 and 43-62 were pending in the instant application. Claims 1-4, 12, 19-20, 43, 52-54, and 58-59 have been amended, claims 5-8, 16, 44-49, 55-57 and 62 have been canceled. New claims 63-66 have been added. Accordingly, claims 1-4, 12, 19, 20, 43, 50-54, 58-61 and 63-66 will be pending after entry of the instant amendment

The Examiner has withdrawn from consideration claims 5-8, 16, 47, 48, 51, 56, 57 and 62 (directed to human and/or rat MEKK1 species; *i.e.*, isoforms). The Examiner is further considering pending generic claims only to the extent that the claims read on mouse MEKK1 species, *i.e.*, isoforms. The Examiner has withdrawn subject matter from consideration based on the fact that a mouse MEKK1 isoform has previously been described in the art. Certain claims have been voluntarily cancelled by Applicant. Applicant has further amended the claims to describe the invention with greater particularity. Applicant respectfully submits that none of the pending generic claims, read on the mouse MEKK1 isoform previously described in the art and respectfully submits that all claims pending after entry of the instant amendment are proper for substantive consideration.

Support for the new and amended claims can be found throughout the specification and claims as originally-filed. In particular, support for the amendment to claims 43 and 52 and for new claims 63-64 can be found in the specification at least, for example, at page 6, lines 31-35; at page 7, lines 18-20; at page 8, lines 18-19; at page 13, lines 26-29; at page 14, line 1 through page 15, line 8; in Example 1; and in Figure 7. Further support for new claims 63-64 can be found in the specification at least, for

example, at page 12, lines 16-26; and at page 15, line 25 through page 16, line 21. Support for the amendments to claims 53-54 can be found at least, for example, at page 5, lines 33-35; at page 7, lines 4-20; in Example 2; and in Figure 4.

Attached hereto is APPENDIX A containing a marked-up version of the changes made to the claims by the current amendments. APPENDIX A is captioned "Version With Markings to Show Changes Made". No new matter has been added. The foregoing claim cancellations and/or amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 43-46, 49-50, 52-55 and 58-61 Under 35 U.S.C. § 112

The Examiner has rejected claims 43-46, 49-50, 52-55 and 58-61 under 35 U.S.C. § 112, second paragraph, over the recitation of the phrase "consisting of about . . .". It is the Examiner's position that the phrase renders the claims unclear. Without acquiescing to the rejection, claims reciting the phrase have been cancelled or amended. Applicant accordingly submits that the rejection is rendered moot and requests reconsideration and withdrawal of the rejection.

Rejection of Claims 1-4, 12, 19-20, 43-46, 49-50, 52-55 and 58-61 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-4, 12, 19-20, 43-46, 49-50, 52-55 and 58-61 under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection."

With respect to claims 44-46, 49 and 55, Applicant respectfully submits that the foregoing rejection has been rendered moot in view of the cancellation of these claims. With respect to claims 1-4, 12, 19-20, 43, 50, 52-54 and 58-61, Applicant traverses this rejection for the following reasons.

Example 14 of the *Revised Interim Written Description Guidelines Training Materials* provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "***[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.***" 63 FR 32,639 (June 15, 1998).

Similarly, in the present case, the claims are directed to genera and/or subgenera which are structurally and functionally described in the instant specification and for which an adequate representative number of species are described.

In particular, claim 1 and corresponding dependent claims (as amended) recite a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3. Claim 43 and corresponding depending claims (as amended) recite nucleic acid molecules encoding MEKK1 apoptotic fragments having 95% global identity to the apoptototic fragment consisting of amino acid residues 875-1493 of SEQ ID NO:4. Claim 52 and corresponding dependent claims (as amended) recite nucleic acid molecules encoding protease-resistant MEKK1 proteins, the protease-resistant MEKK1 having 95% global identity to SEQ ID NO:4 and at least one mutation in the caspase cleavage site. New claim 65 and corresponding dependent claims are directed to nucleic acid molecules encoding a protein having 95% global identity to the MEKK1 protein set forth as SEQ ID NO:4 and a MEKK1 biological activity. Applicants have taught conserved residues between at least three MEKK1 proteins, see *e.g.*, Figures 3, 7 and 8, as well as conserved

caspase cleavage sites within said MEKK1 proteins. Further, Applicants teach the existence of regulatory, catalytic, and/or apoptotic domains in the proteins encoded by the claimed nucleic acid sequences (see *e.g.*, page 17, line 3, through page 18, line 2). Applicants further teach methods of measuring the activity of the proteins encoded by the claimed nucleic acid molecules (see, *e.g.*, Examples 1-2).

Thus, based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicant was in possession of the claimed invention at the time of filing. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

The Examiner has further rejected claims 1-4, 12, 19-20, 43-46, 49-50, 52-55 and 58-61 under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is not enabling.

With respect to claims 44-46, 49 and 55, Applicant respectfully submits that the foregoing rejection has been rendered moot in view of the cancellation of these claims. With respect to claims 1-4, 12, 19-20, 43, 50, 52-54 and 58-61, Applicant traverses this rejection for the following reasons.

The claims have been amended to more distinctly describe the instant invention as discussed above. The specification discloses various nucleotide sequences encoding MEKK1 proteins, protease-resistant MEKK1 proteins and MEKK1 apoptotic fragments, and further provides guidance for the identification, selection, and isolation of additional nucleic acid molecules encoding said MEKK1 proteins and/or apoptotic fragments thereof. In the instant specification, both the structure and function of these MEKK1 proteins and/or fragments are described in detail. The specification further provides guidance in isolating naturally occurring variants and creating non-naturally occurring variants of MEKK1 proteins and/or fragments, such as by making nucleic acid deletions, or substitutions. Moreover, the specification teaches various ways to assay for MEKK1 activities that can be used to identify MEKK1 variants and/or fragments.

To fulfill the enablement requirement under 35 U.S.C §112, first paragraph, the specification must describe how to make and use the claimed invention. However, it is well known that enablement is not precluded by the necessity for some experimentation,

such as routine screening (see, e.g., *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). The pending claims require that the nucleic acids encode proteins or fragments proteins have specific structural features and specific functional features. The specification provides sufficient guidance to the skilled artisan to make such proteins, including disclosing which regions of MEKK1 are important for functional activity and which regions may be amenable to alteration, and how to determine the functional activity of the encoded variants. Accordingly, any experimentation that may be required to make the claimed MEKK1 proteins or fragments constitutes routine, not undue, experimentation.

In view of all of the foregoing, it is evident that making and testing molecules that are 95% identical to the molecules of the present invention having the recited functional attributes would require no more than routine experimentation for the ordinary skilled artisan. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 1-4, 12 and 19-20 Under 35 U.S.C. 102(b)

The Examiner has rejected claims 1-4, 12 and 19-20 under 35 U.S.C. 102(b) as being anticipated by Johnson WO 95/28421 or Johnson WO 94/24159. In particular, the Examiner relies on the Johnson references as teaching MEKK1 isoforms (*i.e.*, mouse MEKK1s) falling within the scope of the enumerated claims. Applicant traverses the rejection for the following reasons.

Claim 1 has been amended to recite a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3. Applicant submits that the amendment renders moot the rejections under 35 U.S.C. 102(b) as the MEKK1 isoforms described in the Johnson references do not comprise the nucleotide sequence of SEQ ID NO:3. New claim 63 and corresponding dependent claims are directed to nucleic acid molecules encoding MEKK1 proteins having at least 95% global identity to SEQ ID NO:4. Applicant submits that the MEKK1 isoforms described in the Johnson references do not have the required 95% identity when aligned over the entire length of the reference sequence, *i.e.*, when globally aligned to SEQ ID NO:4. As such, Applicant submits that

the Johnson references fail to teach or suggest the MEKK1 nucleic acid molecules as presently claimed. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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Dated: November 22, 2002

APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An isolated nucleic acid molecule [selected from the group consisting of:

a) a nucleic acid molecule] comprising the nucleotide sequence of SEQ ID NO:3 or a complement thereof[;

b) a nucleic acid molecule comprising a fragment of at least 100 contiguous nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:3 or a complement thereof;

c) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:4;

d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:4;

e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:3 under stringent conditions; and

f) a nucleic acid molecule which is antisense to the coding strand of a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:3].

2. (Amended) The nucleic acid molecule of [claim 1] any one of claims 1 and 63-65, further comprising vector nucleic acid sequences.

3. (Amended) The nucleic acid molecule of [claim 1] any one of claims 1 and 63-65, further comprising nucleic acid sequences encoding a heterologous polypeptide.

4. (Amended) A host cell which contains the nucleic acid molecule of [claim 1] any one of claims 1 and 63-65.

12. (Amended) A method for producing a [polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:4;

b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:4; and

c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:3 under stringent conditions;]

MEKK1 protein comprising culturing the host cell of claim 4 under conditions in which the nucleic acid molecule is expressed.

19. (Amended) A method for detecting the presence of a MEKK1 nucleic acid molecule in a sample comprising:

a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule of any one of claims 1 and 63-65; and

b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a MEKK1 nucleic acid molecule in the sample.

20. (Amended) A kit comprising a compound which selectively hybridizes to [a] the MEKK1 nucleic acid molecule of any one of claims 1 and 63-65 and instructions for use.

43. (Amended) An isolated nucleic acid molecule [consisting of a nucleotide sequence having at least 75% homology to a nucleotide sequence consisting of about nucleotides 2637-4493 of SEQ ID NO:3, wherein said nucleic acid molecule] which encodes an active fragment of MEKK1 that mediates apoptosis, said fragment having 95% sequence identity to residues 875-1493 of SEQ ID NO:4, wherein % identity is determined over the entire length of residues 875-1493 of SEQ ID NO:4.

52. (Amended) An isolated nucleic acid molecule encoding a protease-resistant MEKK1 protein, wherein the protease resistant MEKK1 protein comprises an amino acid sequence having at least [75% homology] 95% identity to the amino acid sequence of SEQ ID NO:4, wherein % identity is determined over the entire length of SEQ ID NO:4, and wherein at least one codon of the nucleic acid molecule encoding an amino acid equivalent to at least one of amino acids 871-874 of SEQ ID NO:4 is mutated such the encoded MEKK1 protein is resistant to proteolysis by a caspase after an amino acid equivalent to amino acid [871-]874 of SEQ ID NO:4.

53. (Amended) The nucleic acid molecule of claim 52, wherein [the MEKK1 protein comprises an amino acid sequence having at least 85% homology to the amino acid sequence of SEQ ID NO:4] at least one codon is mutated to encode an alanine residue.

54. (Amended) The nucleic acid molecule of claim 52, wherein [the MEKK1 protein comprises an amino acid sequence having at least 95% homology to the amino acid sequence of SEQ ID NO:4] each codon is mutated to encode an alanine residue.

58. (Amended) An expression vector comprising the nucleic acid molecule of [claim 43] any one of claims 43, 50 and 51.

59. (Amended) An expression vector comprising the nucleic acid molecule of [claim 52] any one of claims 52-54.